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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
08/532,384	09/22/95	ARTAVANIS-TSAKONAS S	7326-035

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EXAMINER	
EYLER, Y	
ART UNIT	**PAPER NUMBER**
1642	19

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Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application No. 08/532,384	Applicant(s) Artavanis-Tsakonas
	Examiner Yvonne Eyler	Group Art Unit 1642

☒ Responsive to communication(s) filed on *Dec 23, 1998*.

☒ This action is **FINAL**.

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire *3* month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☒ Claim(s) *90, 98, 101, 103-106, and 109-112* is/are pending in the application.

Of the above, claim(s) *101, 104, 105, 111, and 112* is/are withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) *90, 98, 103, 106, 109, and 110* is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐approved ☐disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____.

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____.

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☐ Notice of References Cited, PTO-892

☒ Information Disclosure Statement(s), PTO-1449, Paper No(s). *17*

☐ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

Response to Amendment

1. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

2. Claims 90, 98, 101, 103-106, and 109-112 are pending. Claims 90, 98, 103, 106, 109, and 110 are under consideration in the application.

Specification

3. The objection to the disclosure is withdrawn in light of the amendments thereto.

Claim Objections

4. The objection to claim 90 is withdrawn in light of the amendments thereto.

Information Disclosure Statement

References CF, CG, and CV of the supplemental IDS filed on 12/23/98 have been considered but are lined through so that they will not be printed upon issuance of a patent.

Claim Rejections Maintained and New Grounds of Rejection:

5. The rejection of Claims 90, 98, 103, 106, 109, and 110 under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention is maintained.

With regard to the recitation of "the manipulation of cell differentiation," applicant presents the Webster's dictionary definition in support that one of skill in the art would know what "manipulation of cell differentiation" means. This is not found to be persuasive. The dictionary definition conveys that "manipulation" means to control, operate, or influence. Thus applicant concludes that one of skill in the art would know that anything that influences cell differentiation, either to alter it or maintain it, is encompassed. This is not found to be persuasive because there is insufficient description of the metes and bounds of the claimed invention as made of record and the definition of manipulation does not clarify the metes and bounds of the claimed invention. The specification does not identify what constitutes manipulated, influenced, altered, or maintained differentiation and what does not. The claim language is circular claiming a method of manipulating cell differentiation by applying a molecule identified by it's ability to manipulate cell differentiation by determining that it manipulates cell differentiation, yet the actions or parameters which define and facilitate identification of manipulated (or influenced) cell differentiation are not set forth either in the specification or the claim language.

The recitation "Notch function" is also maintained to be vague and indefinite. Applicant argues that it is known in the art that Notch functions as a signal transducer and as a receptor for signal transducing signal ligands. Support is cited at page 16 of the specification. Applicant concludes that Notch function is any activity of the protein within the signal transduction pathway which can be measured. This is not found to be persuasive because it remains unclear what measurable action or parameter is considered a "function" of Notch. While Notch would appear

to "function" in signal transduction, the identifiable and measurable activities which are definitive of "function" are not disclosed with the exception of a single example of binding to Delta. Apparently, however, Notch function encompasses any activity within the transduction pathway, even though such is not defined and not readily identifiable by the instant specification. Thus, while the claim recitation encompasses any function, it is not clear what measurable parameters (other than binding to Delta) are definitive of Notch "function" and what measurable parameters are not. One solution to clarify the claim language would be to substitute -binding to Delta- in place of "function."

Finally, it is maintained that the recitation of "Notch-group" of genes is vague and indefinite. Applicant argues that one of skill in the art would know what is meant because the specification teaches that such genes are identified by molecular and genetic interactions. Applicant argues that the term interaction would be clearly interpreted to mean "to act on" and thus one of skill in the art would know that any gene which acts on a Notch group member would be considered to be a Notch group member. Applicant illustrates by discussing Delta and SuH, one of which binds to Notch and the other which is subsequently translocated to the nucleus due to Delta binding. These arguments have been considered but are not found to be persuasive. It remains unclear what interaction or actions on other unidentified members are definitive of a "Notch-group" gene. The identification of Notch group members by there actions upon Notch group members is circular and does not clarify what defines a Notch group member. There are no definitive physical or structural characteristics associated with Notch group members provided.

Further, the measurable activities which are indicative of a definitive interaction are not provided nor are the parameters of an interaction (or an action upon) provided. For example, apparently SuH is considered a Notch group protein because it is translocated to the nucleus after Delta binds to Notch, yet the action that SuH takes on another Notch group member is not disclosed, thus SuH does not meet the current definition of a Notch group member as one that interacts with other Notch members. Thus it is maintained that it is not clear and one of ordinary skill would not understand what molecules are encompassed as a Notch group molecule and what molecules are not nor how this is definitively determined.

6. The rejection of Claims 90, 98, 103, 106, 109, and 110 under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention is maintained.

Applicant argues that Notch plays a role in cell differentiation and that manipulation of Notch function would be expected to manipulate cell differentiation. Applicant cites several references in support of the predictability of cell differentiation manipulation. Applicant further argues that the definition of "Notch function" is not unclear and reiterates the reasoning discussed supra with regard to the rejection under 112 second paragraph and concludes that one of skill would therefore know how to determine if Notch function were promoted. Applicant further argues that the measurement of cell differentiation is art standard and thus one of skill would be

enabled to determine if differentiation were manipulated. Applicant argues that the specification discloses molecules which promote Notch function including proteins, derivatives, and portions of toporythmic proteins thus enabling any molecule that promotes Notch function. Applicant argues that dosage optimization is routine in the art. Applicant argues that while predictability of the art is a factor to be considered, that the predictability of the result of an experiment is not, citing *In re Angstadt* in support. Applicant finally summarizes the similarities between Notch proteins in differing species, that Notch is associated with cell fate, and that binding characteristics are maintained from different species and refers to two declarations of Dr. Artavanis-Tsakonas. Applicant also points to increased expression of Notch associated with malignancy.

These arguments have been considered but are not found to be persuasive. Applicant is reminded that the invention must be enabled at the time of filing. Although applicant can present information regarding the enablement of a claimed invention after filing, the methods and compounds must have been taught at the time of filing. While the cited references provide evidence that activation of Notch, through ligand binding, as measured by increased expression, inhibits cell differentiation, each of the 7 references are post-filing date references and rely on material, methods, and disclosures that were not available to one of skill in the art from the instant specification or the prior art at the time the invention was filed. At the time of filing, the role of Notch in cellular differentiation was not known or predictable in the art, as made of record in the Office Action of 6/23/98. The specification discloses the regions of Notch necessary for Delta binding and cell aggregation but provides insufficient objective evidence that Delta binding was

known to or reasonably expected to promote the activity of Notch in the regulation of cell differentiation. The prior art available at the time of filing did not support predictability of the manipulation of cell differentiation by promoting Notch function via Delta binding. Sun et al. (Development 124:3439-3448, 1997) was previously cited for teaching that in some instances, binding of Delta functions as an antagonist of Notch and that the precise role of Notch and Delta proteins or their interactions in cell fate and differentiation was undefined (see the entire article, but especially page 3439). Furthermore, even if the cited references were available at the time of filing, the teachings of the references, single or in combination, are not commensurate in scope with the claimed invention. The post filing date references teach activation of Notch by truncation, overexpression, or binding by the ligands Jagged, Delta, or Serrate. No other molecules, fragments, derivatives or homologs are disclosed nor is guidance regarding their selection provided. Cell differentiation is taught to be inhibited or prevented. No other manipulations are evidenced or guidance provided regarding the determination of any other measurable manipulations of differentiation. No other functions of Notch in signal transduction are provided or measured. Thus, the evidence provided by the references, even if applicable, is not fully enabling and commensurate in scope with the invention as broadly claimed.

Applicants arguments regarding Notch function are not found to be persuasive. That Notch function is vague and indefinite has been maintained as detailed supra. Further, the specification discloses regarding Notch binding to Delta and resultant cell aggregation but does not provide guidance or objective evidence commensurate in scope with the claimed invention

which includes any function, defined or not. Illustrative of this point is the argument that Notch functions in signal transduction are encompassed. No evidence or guidance regarding where or how Notch functions in what signal transduction pathway is provided by the instant specification. There is insufficient guidance provided regarding how a signal (or what signal) is measured. Applicant provides an example of translocation of SuH which is not even contemplated as a function of Notch in the instant specification, thus supporting the grounds of rejection that the specification is not enabling for the full scope of the encompassed invention.

The grounds of rejection that one of skill in the art would not be enabled to measure or determine cell differentiation is withdrawn. The determination of cell differentiation was well know in the art at the time of filing as applicant has indicated. It is noted, however, that Sakano et al is not prior art.

Applicants argument regarding the enablement of any molecule which promotes Notch function is not found to be persuasive. Applicant relies on the disclosure on pages 11-12 of the specification that derivatives and portions of Delta and Serrate are contemplated. Initially, it is noted that the scope of the claimed molecule encompasses far more than derivatives of Delta or Serrate, including any molecule of any structure or composition. There is insufficient guidance regarding the requirements of such a molecule which are correlated with promotion of Notch "function." Furthermore, while derivatives or portions of Delta or Serrate are specifically mentioned, there is insufficient guidance regarding what portions or regions are necessary and sufficient for not only binding but also for promotion of Notch "function." As made of record in

the Office Action of 6/23/98, the structure of a molecule and/or the amino acid sequence of a protein determines its functional properties, and predictability of which structures or amino acids within a protein's sequence or molecules chemical structure result in the claimed activity is extremely complex, and well outside the realm of routine experimentation. Fehon et al. (Cell 61:523-534, 1990-IDS-BL) teach that an "understanding of the precise nature of the processes that underlie genetic interaction [of Notch] requires a knowledge of the biochemical properties of the protein products of the genes in question." Since detailed information regarding the structural and functional requirements of this protein or molecule are lacking, it is unpredictable as to which amino acid sequences, fragments, or chemical structures if any, meet the limitations of the claim. Furthermore, while recombinant and screening techniques are available, it is not routine in the art to screen large numbers of proteins and molecules where the expectation of obtaining a stated activity is unpredictable based on the instant disclosure. Therefore, one of ordinary skill would require guidance, such as information regarding the extent of substitution and the location and the specific amino acid changes which would result in the preservation of the stated activity. Therefore, it would require undue experimentation by one of skill in the art to practice the invention as claimed without further guidance from the instant specification.

Applicant argues that optimization of dosage is routine in the art, however, the basis of the rejection and the teachings of Fehon et al. in which "dosage" was mentioned do not address the dosage of a compound to be administered. Fehon et al. were cited for teaching that in the case of Notch and Delta, not only interaction, but dosage is important (see page 523). In this instance,

dosage does not refer to the administration of a compound to cell or organism but rather refers to the ratio and location of active Notch and Delta. Thus, even if a derivative or portion of Delta were identified, the mere binding to Notch does not necessarily predict promotion of "function" since the ratio would appear to be important as well.

Applicant's argument and citation in support thereof of *In re Angstadt* that predictability of a result versus predictability of the art does not prohibit enablement is not found to be persuasive. Applicant relies on the passages of the opinion addressing the misplaced application of *In re Rainer* 54 CCPA 1445, 377 F.2d 1006, 153 USPQ 802 (1967) and the emphasis of undue experimentation versus any experimentation. The issue, however, under consideration in *In re Angstadt* is "whether in an unpredictable art, section 112 requires disclosure of a test with every species covered by a claim." The court concluded in *In re Angstadt* that since a list of species was provided and guidance was provided regarding how to make and use them, that the requirements of 112 first paragraph were met. The court noted, however, that "each case must be determined on its own facts." In the instant situation, there are no species provided which meet the claim limitations nor is sufficient guidance provided regarding how to make and use molecules as recited with a reasonable certainty that use of the molecule would promote Notch function and manipulate differentiation. The specification discloses that Delta binds to Notch, but does not provide sufficient evidence correlating binding to promotion of Notch activity and predictable manipulation of differentiation. Thus, without further guidance and evidence regarding molecules

which promote Notch function and manipulate differentiation, it is maintained that it would require **undue** experimentation to practice the invention as claimed.

Finally, the similarities noted by applicant between Drosophila Notch and human Notch are not found to be persuasive. Applicant emphasizes the similarity between the two proteins and their characteristics and points to the fact that Drosophila Notch plays a role in cell fate, equating cell fate with differentiation, citing the declaration by Dr. Artavanis-Tsakona in support. The copy of the "second declaration" of Dr. Artavanis-Tsakonas states regarding the similarities between the ligand binding domains of Notch from human, rat, Xenopus, and Drosophila. However, the binding by Notch is not at question, rather, what is at issue is the predictable promotion of Notch and resultant manipulation of differentiation by a molecule. Ligand binding by Notch does not address this question. Dr. Artavanis-Tsakonas further declares (providing a manuscript in support) and applicant argues regarding the role of Notch in development and cell fate (differentiation fate), i.e. the choice of a cell to differentiate into one tissue type versus another in response to signals and interactions with other cells. As previously made of record, however, cell fate and cell differentiation are not equivalent concepts. "Differentiation is defined as a "process of development in a multicellular organism by which cells become specialized for particular functions. [Differentiation] Requires that there is selective expression of portions of the genome; the fully differentiated state may be preceded by a stage in which the cell is already programmed for differentiation but is not yet expressing the characteristic phenotype (determination)." (The Dictionary of Cell Biology, p.61, 1989) Thus, a gene or protein which manipulates or affects

determination in not necessarily capable of manipulating or affecting the process of differentiation." Thus, while Notch may influence determination or cell fate in Drosophila, and while Drosophil, rat, mouse, Xenopus, and human Notch may be similar, this does not address and is not predictive of the use of molecules to promote Notch function and influence cell differentiation in either Drosophila or humans. Dr. Artavanis-Tsakonas referral to uses of Notch to generate antibodies or detect ligand binding is not found to be relative to the instantly claimed method. That Notch is expressed at a higher level in malignant tissue which entails a disturbance in differentiation (supported by the copy of the "fourth declaration" of Dr. Artavanis-Tsakonas) is also not found to be predictive that promotion of Notch function manipulates differentiation. The association of an increased expression of a molecule in malignant tissue is not directly correlative with a causative role. Correlation between Notch expression and malignancy does not necessarily correlate Notch expression with mechanisms of differentiation in malignant tissue, and it is not predictable that Notch is responsible for the disturbance in differentiation of malignant cells.

Thus, for reasons detailed above, it is maintained that it would require undue experimentation by one of skill in the art to practice the instant invention.

NO CLAIM IS ALLOWED.

7. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Yvonne Eyler, Ph.D. whose telephone number is (703) 308-6564. The examiner can normally be reached on Monday through Friday from 830am to 630pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Paula Hutzell, can be reached on (703) 308-2731. The fax phone number for this Group is (703) 305-3014 or (703) 308-4242.

Communications via Internet e-mail regarding this application, other than those under 35 U.S.C. 132 or which otherwise require a signature, may be used by the applicant and should be addressed to [**paula.hutzell@uspto.gov**].

All Internet e-mail communications will be made of record in the application file. PTO employees do not engage in Internet communications where there exists a possibility that sensitive information could be identified or exchanged unless the record includes a properly signed express waiver of the confidentiality requirements of 35 U.S.C. 122. This is more clearly set forth in the Interim Internet Usage Policy published in the Official Gazette of the Patent and Trademark on February 25, 1997 at 1195 OG 89.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Yvonne Eyler

Yvonne Eyler, Ph.D.
Primary Patent Examiner
March 11, 1999